UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/515,276	02/29/2000	Marc R. Montminy	SALK1650-2	1983

30542 7590 11/28/2003

FOLEY & LARDNER
P.O. BOX 80278
SAN DIEGO, CA 92138-0278

EXAMINER	
WORTMAN, DONNA C	
ART UNIT	**PAPER NUMBER**
1648	

DATE MAILED: 11/28/2003

LS

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/515,276	MONTMINY, MARC R.	
	Examiner	Art Unit	
	Donna C. Wortman, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 September 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,12 and 17-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,12 and 17-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Claims 1-7, 12, and 17-33 remain pending and under examination.

Rejections maintained

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written description rejection

Claims 1-7, 12, and 17-33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. The Examiner's reasons for making this rejection are of record in the previous Office action, mailed 12 June 2003, at pages 2-5.

Applicant has reviewed the standards for compliance with the written description requirement under 35 U.S.C. 112, first paragraph, and has pointed out that claims 1-7, 12 and 17 are directed to methods of diabetes treatment; claims 18-24 and 33 are directed to methods for modulating glucose metabolism in an individual; and claims 25-32 are directed to methods of inhibiting the expression of carboxykinase (PEPCK) enzyme in an individual; has questioned whether the written description rejection was in fact intended to apply to all of the claims or only to those specifically directed to diabetes treatment; has asserted that written description does not require a chemical description where the compound can be identified by methods that are both described and enabled; and has pointed out that the specification at page 15-16 describes

antibodies; at page 17 describes peptides; and also mentions adenovirus E1A oncoprotein, all of which are compounds that disrupt CREB:CBP interaction and by so disrupting, inhibit activation of cAMP and mitogen responsive genes. Applicant asserts that the specification thus describes "numerous exemplary compounds."

Applicant's arguments filed 11 September 2003 have been fully considered but they are not persuasive. In the interest of clarifying the record, the Examiner acknowledges that independent claim 1 is drawn to a method for treating an individual suffering from diabetes mellitus, comprising administering an effective amount of a compound which inhibits binding of CREB to CBP; independent claim 12 is drawn to a method for treating an individual suffering from diabetes mellitus comprising administering an effective amount of a compound which disrupts complex comprising cyclic AMP response binding protein (CREB) and CREB binding protein (CBP); independent claim 17 is drawn to a method for treating an individual suffering from diabetes mellitus, comprising administering an effective amount of a compound which disrupts complex comprising cyclic AMP response element binding protein (CREB) and CREB binding protein; independent claim 18 is drawn to a method of modulating glucose metabolism in an individual, comprising administering an effective amount of a compound which inhibits binding of CREB to CBP; and independent claim 25 is drawn to a method for inhibiting expression of phosphoenolpyruvate carboxykinase (PEPCK) enzyme in an individual, comprising administering an effective amount of a compound which inhibits binding of CREB to CBP. It is further noted that claim 33, which depends ultimately from claim 18, recites that "said individual is suffering from diabetes mellitus,"

and that claim 31, which depends ultimately from claim 25, recites that "said individual is suffering from diabetes mellitus." The Examiner confirms that the written description rejection set forth in the previous Office action was intended to apply to all the pending claims, since all the claims either explicitly recite treatment of human diabetes *per se* or encompass treatment of human diabetes, and all the claims require administering to an individual a compound identified by Applicant's method that inhibits binding of CREB to CBP. It is apparent from the specification, e.g., at pages 20-21, that the only context in which "an effective amount" of a compound is to be administered to "an individual" is in the context of treating diabetes. Applicant's argument that written description of a compound does not require a chemical description is not understood, since a functional description of a compound alone does not describe a compound, but only describes its function, and the only function described is that the compound inhibit binding of CREB to CBP. The claims do not recite that antibodies, peptides or adenovirus E1A are administered as a treatment. While it is so that the specification describes certain antibodies and peptides, and mentions adenovirus E1A, as disrupting CREB:CBP interaction, there is no description directed toward "an effective amount" nor of administering an "effective amount" of these types of compounds to an individual, where an effective amount is as defined in the specification:

> As employed herein, the phrase "effective amount" refers to levels of compound sufficient to provide circulating concentrations high enough to modulate the expression of gene(s) mediated by members of the steroid/thyroid superfamily of receptors.

Since CREB:CBP interaction occurs within a cell nucleus, and since there is no description of compounds identified by Applicant's method that are administered to an

individual at levels of compound sufficient to provide circulating concentrations high enough to modulate the expression of gene(s) mediated by members of the steroid/thyroid superfamily of receptors, there is insufficient written description to reasonably convey that Applicant had possession of the claimed invention insofar as drawn to treatment methods.

Enablement rejection

Claims 1-7, 12, and 17-33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons made of record in the previous Office action at pages 6-8.

Applicant has reviewed the standards for enablement under 35 U.S.C. 112, first paragraph; has asserted that Examiner has not addressed "most" of the Wands factors and has offered an alternate analysis of the Wands factors. In particular, Applicant has (1) defined the nature of the invention; argued (2) that the state of the prior art establishes that drugs that affect intracellular events have a beneficial effect on disease treatment, and has cited Rossetti et al., Clin. Invest. Med. 18(4):225-260, 1995, supplied as Exhibit A, and Flatt et al., Biochemical Society Transactions 22:18-23, 1994, supplied .as Exhibit B, to show that reducing hyperglycemia is accepted in the art as an aspect of diabetes treatment; has argued that the Merck Manual generally discusses only long established treatment modes and does not adequately establish the state of the art; cites several patents already of record and points out that none of the patented subject

matter is discussed in the Merck Manual; and asserts that Applicant's method of treating diabetes mellitus would be what one skilled in the art would consider to be a predicable route to treating diabetes. Applicant has asserted (3) that the level of skill in the art is high. Applicant has argued (4) that the art in the relevant field is reasonably predictable, has reviewed the teachings of the instant specification, and has stated that the Examiner "has offered no evidence on this Wands factor." With respect to the amount of direction or guidance present in the specification, Applicant has (5) made reference to the methods for identifying inhibiting compounds as well as the disclosure of routes of administration, methods of formulation, and dosing as disclosed on pages 17-18. Applicant has asserted (6) that working examples are present and has relied upon Mayr et al. and Herzig et al., of record, as serving to prove the truth of statements in the disclosure and as evidence that the claimed invention is enabled. Applicant argued that the issue should not be whether beneficial effects have been obtained but whether the specification enables the skilled artisan to obtain such effects without undue experimentation and has reiterated that reduction in blood glucose levels is considered in the art to be treatment for diabetes. With respect to the amount of experimentation necessary, Applicant has asserted (7) that "there is no reason to believe that useful inhibitors of the CREB:CBP interaction will not be useful when such compounds reach the targeted components (CREB or CBP) in cells" and that only routine experimentation would be needed to identify compounds that function well in this regard. With respect to the inclusion of claims 18-24 and 33, in the enablement rejection previously offered,

Applicant has pointed out that claims 18-24 and 33 and claims 25-32 make no reference to diabetes.

These arguments have been considered but not found persuasive. It is noted that the enablement rejection as previously set forth was based on consideration of the Wands factors and the evidence as a whole, and that the Examiner need not discuss each factor in the written enablement rejection, and need only cite the factors, reasons, and evidence that led the Examiner to conclude that the specification fails to teach how to make and use the claimed invention without undue experimentation (MPEP 2164.04). With respect to (1) and (3), above, the nature of the claimed invention is noted, and it is agreed that the level of skill in the art is high. Addressing Applicant's discussion of the state of the prior art and the material cited in support, (2), it is appreciated that the art recognizes that reducing hyperglycemia by a variety of means, including control of diet, as an aspect of diabetes treatment, and that potential treatments, or new treatments, may not be described in the Merck Manual; however, Applicant has presented no evidence in support of the assertion that Applicant's claimed method of treating diabetes mellitus would be considered by one skilled in the art at the time the invention was made to be "a predicable route to treating diabetes." With respect to the predictability of the art, (4), Applicant's assertion, unsupported by facts, that the art in the field is "reasonably predictable" is not persuasive, and Examiner's remarks in the previous Office action citing Herzig et al. regarding unpredictability and the amount of experimentation remaining in the field nearly four years after Applicant's effective filing date are reiterated here: "The effect of A-CREB on liver gene expression

suggests that CREB **may** constitute an ideal target for therapeutic intervention. Although use of a dominant negative inhibitor such as A-CREB may not be feasible in this regard, small molecules that block CREB phosphorylation or disrupt recruitment of the CREB coactivator CBP (CREB binding protein) **may** prove effective. Such compounds **may** be particularly beneficial as adjunctive therapy in lowering fasting blood glucose levels in type II diabetes." (See Herzig et al., page 182, second column, second full paragraph; emphasis added.) With respect to point (5), it is agreed that Applicant discloses and enables methods for identifying compounds that inhibit CREB:CBP binding. Applicant's disclosure of routes of administration, methods of formulation, and dosing are presented in a general fashion and not directed to methods of treatment with any specific compounds. With respect to (6), in fact, there are no working examples for the claimed invention; only prophetic material regarding treatment is presented. See MPEP 2164.02:

A prophetic example describes an embodiment of the invention based on predicted results rather than work actually conducted or results actually achieved.

There are no working examples for the embodiment of the invention that encompasses treatment methods. When an *in vitro* example in the specification correlates with a claimed method invention, then the *in vitro* example in effect constitutes a "working example." If there is no correlation, then the examples do not constitute "working examples." The *in vitro* examples involving inhibition of CREB:CPB involve microinjection of antiserum into NIH3T3 cells (Examples II-IV). There is no indication that the art of record recognizes that microinjection of antibodies into cultured cells reasonably correlates with a treatment method with an effective amount of a compound

that inhibits CREB:CBP, and Applicant has not established that disruption of CREB:CBP complex caused by microinjecting antiserum into cultured cells provides a basis for predicting success for treatment of individuals according to the claimed invention. Addressing (7), above, and considering the evidence as a whole, the specification as filed is not seen to enable one of skill in the art at the time the invention was made to practice the invention as claimed without undue experimentation.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Donna C. Wortman, Ph.D. whose telephone number is 703-308-1032 until 08 January 2004 and 571-272-0913 after that date. The examiner can normally be reached on Monday-Thursday, 7:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 703-308-4027 until 26 January 2004 and

571-272-0902 after that date. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Donna C. Wortman, Ph.D.
Primary Examiner
Art Unit 1648

dcw